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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ANDERSON, REBECCA L	

ART UNIT	PAPER NUMBER
1626	

DATE MAILED: 09/01/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/712,799	KOR ET AL.	
	Examiner	Art Unit	
	Rebecca L. Anderson	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 June 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 22-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-21* is/are rejected.

7)☒ Claim(s) *1-10 and 17* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 November 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/12/03, 4/29/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-27 are currently pending in the instant application. Claims 11-16 and 22-27 are withdrawn from consideration as being for non-elected subject matter, claims 1-10 and 17 are objected and claims 1-10 and 17-21 are rejected.

Election/Restrictions

Applicant's election without traverse of Group I in the reply filed on 19 June 2006 is acknowledged.

Claim Objections

Claims 2-10 and 17 are objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP 706.03(k). Each of claims 1-10 and 17 claim the crystalline Form VI of carvedilol. While claims 1-9 and 17 recite certain X-ray diffraction, DSC thermogram data, FTIR spectrum data, refer to figures or include the process for preparing the compound, the data recited is considered properties of the compound and are inseparable from the compound itself. Furthermore, page 4 of the instant specification defines form VI as having all of the properties as claimed in claims 1-9. Therefore, claims 2-10 and 17 are considered duplicate claims of claim 1. This objection can be overcome by deleting claims 2-10 and 17 and inserting the date from claims 2-10 and 17 into claim 1.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 18-21 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As stated in the MPEP 2164.01 (a), "There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue."

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

In the instant case, Claims 18-21 claim compositions comprising crystalline solid of carvedilol form VI, such as an oral dosage form of a tablet.

The nature of the invention

A pharmaceutical composition comprising Form VI carvedilol.

The state of the prior art

The state of the prior art is that the preparation of pharmaceutical compositions requires, milling, adding excipients, surfactants, etc. The process of preparing a pharmaceutical composition, such as milling, will cause a specific crystalline form, if in the metastable state to resort back to the most thermodynamically stable form which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32). It is also the state of the prior art that an acceptable carrier for a pharmaceutical formulation can be water. Dissolving a specific crystalline form in water, creating an aqueous solution, would put the compound in its free form and not in a crystalline form with a specific X-ray diffraction pattern.

The predictability or lack thereof in the art

The predictability or lack thereof in the art is that a metastable compound will resort back into its most thermodynamically stable form which would have a different X-ray diffraction pattern. Also, a solution prepared from a specific crystalline form and water would contain the free form of the compound.

The amount of direction or guidance present and the presence or absence of working examples

While the specification has provided processes for the preparation of the crystalline form VI, the specification does not provide examples of processes for preparing pharmaceutical compositions utilizing the crystalline form VI. The specification fails to provide the steps of ensuring that the pharmaceutical compositions

will maintain the specific forms as found in the specification and will not resort back to the free form or the most thermodynamically stable form of the compound.

The breadth of the claims

A pharmaceutical composition comprising Form VI carvedilol.

The quantity of experimentation needed

The quantity of experimentation needed is undue. One of ordinary skill in the art, without direction, would be unable to maintain a specific metastable crystalline form upon preparation into a pharmaceutical composition which may require milling or formation of a solution.

The level of the skill in the art

While the level of skill in the art is high, one of skill in the art would be unable to maintain a specific metastable crystalline form upon the preparation of a pharmaceutical composition without direction and guidance which is not found in the instant specification. One of skill in the art would expect the pharmaceutical composition to contain the most thermodynamically stable form of the compound or the free form of the compound.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 4, 6 (dependent claims 7 and 8) and claim 9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically claims 4, 6 and 9 refer to figures 1, 3 and 2 in the instant specification. Claims must

stand alone to define the invention and incorporation into claims by express reference to specification and/or drawings is not permitted. One must refer back to the specification to determine what applicant is claiming by referring to the figures 1, 2 and 3 of the instant specification. It is suggested that applicant insert the data from figures 1, 2 and 3 into the claims.

Claims 1, 2, 5-10 and 17-21 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. According to Brittain,

> For routing work...one typically compares the powder pattern of the analyte to that of reference materials to establish polymorphic identity. Since every compound produces its own characteristic powder diffraction pattern owing the unique crystallography of its structure, powder X-ray diffraction is clearly the most powerful and fundamental tool for a specification of the polymorphic identity of the analyte. Moreover, the USP general chapter on X-ray diffraction states that the identity is established if the scattering angles of the ten strongest reflections obtained for an analyte agree to within +/- 0.20 degrees with that of the reference material, and if the relative intensities of these reflections do not vary by more than 20 percent. (see Brittain in Polymorphism in Pharmaceutical Solids, p.236).

Claims 1, 2, 5-10 and 17-21 fail to recite any X-ray diffraction peaks or recite only a minimum of 4 peaks. The recitation of 4 or less peaks is not specific enough to particularly point out and distinctly claim the product that Applicant regards as his invention. The claims do not conform to the general practice in the art according to Brittain, i.e. including at least data for the 10 strongest peaks. Claims 1, 2, 5-10 and 17-21 do not contain any of the physical data that particularly points out and distinctly claims the product that Applicant regards as his invention, i.e. no claim provides at least the 10 strongest peaks of the X-ray diffraction data. For example, without this physical data, it is impossible to distinguish applicants claimed crystalline form from any other

crystalline form of the prior art, since there is no data in the claims to distinguish applicants' crystalline form from any other crystalline form. Also, sometimes the differences in the diffraction patterns of different polymorphs are relatively minor, and must be very carefully evaluated before a definitive conclusion is reached (US Pharmacopia, page 1843). It is suggested that the claims be amended to include at least 10 of the strongest peaks of the x-ray diffraction data for form III. However additional data such as the chemical name of the compound melting temperature, DSC thermogram data and FTIR spectrum data should also be included in order to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-10 and 17-21 are rejected under 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Specifically, claims1-10 and 17-21 are directed to products of a crystalline solid of carvedilol or a solvate thereof with the specific PXRD pattern data, DSC thermogram data and FTIR spectrum data. However, the claims are considered indefinite as the crystalline solid of carvedilol and the solvate thereof would have different x-ray diffraction patterns. There can be multiple forms of a solid in existence and these polymorphs are created by varying crystallization processes which began with varying starting materials, utilize varying solvents, varying temperatures and varying reaction times. Furthermore, in addition to exhibiting polymorphism, many compounds form crystalline solvates in which the solvent molecule is an integral part of the crystal structure. Just as every polymorph has its one

characteristic X-ray diffraction patter, so does every solvate. (US Pharmacopia #23, page 1843). This rejection can be overcome by deleting the phrase "or a solvate thereof".

Claim 10 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In regards to the chemical name of the carvedilol Form VI, it is noted that while the inventor may be his/her own lexicographer, claim 10 does not contain any of the physical data that particularly points out and distinctly claims the product that Applicant regards as his invention, i.e. the claim does not provide at least the 10 strongest peaks of the X-ray diffraction data for Form VI. Form VI is not a limiting element and does not define a difference in the carvedilol. Form VI is not a common well recognized term in the art to define anything. While Form VI is a term defined by the inventors, the definition is found in the instant specification as the PXRD, DSC thermogram and FTIR spectrum data. It is this data that distinguishes applicants' invention from the prior art and not the term Form VI. For example, without PXRD data in the claim 10, it is impossible to distinguish applicants Form VI from any other crystalline carvedilol of the prior art, since there is no data in the claims to distinguish applicants' crystalline form any other crystalline form of the compound.

Prior Art Rejections

In regards to applicants compound claims 1-10 and 17, the prior art references of Chen, Wei-Min et al.; US Patent No. 4,503,067; and EP 0918055, while not providing applicants' instant X-ray diffraction data, do name crystalline carvedilol, which puts this

product in the public domain. As these forms differ from the claims in that the references are silent on the crystalline form, applicant must show that their crystalline form really is different from any of the ones prepared in the prior art. MPEP 2112 states: "Something which is old does not become patentable upon the discovery of a new property. The claiming of a new use, new function or unknown property which is inherently present in the prior art does not necessarily make the claim patentable. In re Best, 562 F.2d 1252, 1254, 195 USPQ 430, 433 (CCPA 1977)." In this case, the "unknown property" is the particular crystalline form. This is unknown because the references are silent on this property. MPEP 2112 goes on to state: "A rejection under 35 USC 102/103 can be made when the prior art product seems to be identical except that the prior art is silent as to an inherent characteristic. Where applicant claims a composition in terms of a function, property or characteristic and the composition of the prior art is the same as that of the claim but the function is not explicitly disclosed by the reference, the examiner may make a rejection under both 35 USC 102 and 103, expressed as a 102/103 rejection." Again, the "characteristic" which the prior art is silent on is the crystalline form.

This is not an ordinary inherency situation where it is not explicitly stated what the product actually is. Here the reference explicitly teaches exactly what the compound is. The only difference is a characteristic about which the reference happens to be silent. Se also Ex parte Anderson, 21 USPQ 2nd 1241 and 1251, discussion of Rejection E. There, the decision states, "There is ample precedent for shifting the burden to an applicant to reproduce a prior art product whose final structure or

properties are, at least, in part determined by the precise process used in its manufacture." (page 1253). The "properties' branch of that statement applies here. Applicants are reminded that the PTO has no testing facilities.

It is also noted that the product-by-process of claim 17, the crystalline carvedilol of claim 1 is not limited by the process of claim 11 and is rejected over prior art which provides crystalline carvedilol.

The composition claims 18-21 are rejected under 35 USC 102 as the prior art references disclose compositions comprising applicants' instantly claimed invention as it is the state of the prior art that the preparation of pharmaceutical compositions requires, milling, adding excipients, surfactants, etc. The process of preparing a pharmaceutical composition will cause a specific crystalline form, if in the metastable state, to resort back to the most thermodynamically stable form, which is the form with the lowest vapor pressure. Polymorphs tend to convert from less stable to more stable forms (Rouhi, page 32).

Claim Rejections - 35 USC § 102

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-10 and 17 are rejected under 35 U.S.C. 102(b) as being anticipated by CHEN, Wei Min et al.

CHEN, Wei Min et al. discloses crystalline carvedilol on page 325 and in figure 1, page 328.

Claims 1-10 and 17-21 are rejected under 35 USC 102(b) as being anticipated by US Patent No. 4,503,067.

US Patent No. 4,503,067 discloses pharmaceutical compositions on column 4, for example, in tablets. Example 2, column 5 discloses crystalline carvedilol which is obtained from recrystallization with ethyl acetate.

Claims 1-10 and 17-19 are rejected under 35 USC 102(b) as being anticipated by EP 0918055.

EP 0918055 discloses pharmaceutical use on page 2 as a drug having antihypertrensive activity. Examples 6 and 7 and 8, pages 111, disclose crystalline carvedilol which is recrystallized from ethyl acetate.

Claims 18-21 are rejected under 35 USC 102(b) as being anticipated by EP 0893440.

EP 0893440 discloses carvedilol of form I and II on page 3. Pharmaceutical compositions are disclosed on pages 2 and 3, such as tablets, along with in claim 6, see page 4.

Claims 18-21 are rejected under 35 USC 102(b) as being anticipated by WO 99/05105.

WO 99/05105 discloses carvedilol of form I and II on pages 5 and 6. Pharmaceutical compositions are disclosed on page 4, such as tablets, along with in claim 6, page 9.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States

> only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 18-21 are rejected under 35 U.S.C. 102 (a) and (e) as being anticipated by WO 02/00216.

WO 02/00216 discloses crystalline carvedilol of form III, IV and V and the solvate of methyl-ethyl-ketone) on pages 5, 15 and 16. Pharmaceutical compositions containing carvedilol are disclosed on pages 17-18, such as tablets.

Claims 18-19 are rejected under 35 USC 102(e) as being anticipated by US Pre-Grant Publication No. 2004152756.

US Pre-Grant Publication No. 2004152756 discloses crystalline carvedilol form III and pharmaceutical compositions on page 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over CHEN, Wei-Min et al.

Determining the scope and contents of the prior art

CHEN, Wei Min et al. discloses crystalline carvedilol on page 325 and in figure 1, page 328.

Brittain teaches us that it is a well known fact that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice." Thus, *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims. Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2).

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare the crystalline form as instantly claimed in claims 1-10 and 17 since the prior art reference discloses the formula of figure 1. One would be motivated to prepare the instantly claimed invention because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction patter, melting point etc. (see Brittian p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268 and Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom,

are unpatentable. The instant specification and claims claim a known compound, which is ***the same pure substance*** as the prior art, only *having different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p. 1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of known compounds would have been suggested to one skilled in the art. One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of the known compound would have been suggested to one skilled in the art. The compounds are of the same identical formula, the difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable

unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

The instant claims are claiming a product which is the same pure substance as the prior art, and only has different arrangements and/or different conformations of the molecules without any disclosure of any unexpected properties. The mere differences in the physical properties are well known conventional variations for the same pure substance and are prima facie obvious over the prior art.

Claims 1-10 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over US Patent No. 4,503,067.

Determining the scope and contents of the prior art

US Patent No. 4,503,067 discloses Example 2, column 5 which discloses crystalline carvedilol which is obtained from recrystallization with ethyl acetate.

Brittain teaches us that it is a well known fact that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice." Thus, *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray

diffraction pattern of the instant claims. Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2).

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare the crystalline form as instantly claimed in claims 1-10 and 17 since the prior art reference discloses the formula of figure 1. One would be motivated to prepare the instantly claimed invention because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction patter, melting point etc. (see Brittian p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268 and Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom; are unpatentable. The instant specification and claims claim a known compound, which is ***the same pure substance*** as the prior art, only *having different arrangements and/or*

different conformations of the molecule. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p. 1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of known compounds would have been suggested to one skilled in the art. One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of the known compound would have been suggested to one skilled in the art. The compounds are of the same identical formula, the difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

The instant claims are claiming a product which is the same pure substance as the prior art, and only has different arrangements and/or different conformations of the molecules without any disclosure of any unexpected properties. The mere differences in the physical properties are well known conventional variations for the same pure substance and are prima facie obvious over the prior art.

Claims 1-10 and 17 are rejected under 35 USC 103(a) as being unpatentable over EP 0918055.

Determining the scope and contents of the prior art

EP 0918055 discloses Examples 6 and 7 and 8, pages 111, which disclose crystalline carvedilol which is recrystallized from ethyl acetate.

Brittain teaches us that it is a well known fact that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice." Thus, *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims. Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the

molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2).

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare the crystalline form as instantly claimed in claims 1-10 and 17 since the prior art reference discloses the formula of figure 1. One would be motivated to prepare the instantly claimed invention because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction patter, melting point etc. (see Brittian p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268 and Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant specification and claims claim a known compound, which is ***the same pure substance*** as the prior art, only *having different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p. 1-2), i.e.

prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of known compounds would have been suggested to one skilled in the art. One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of the known compound would have been suggested to one skilled in the art. The compounds are of the same identical formula, the difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

The instant claims are claiming a product which is the same pure substance as the prior art, and only has different arrangements and/or different conformations of the molecules without any disclosure of any unexpected properties. The mere differences

in the physical properties are well known conventional variations for the same pure substance and are prima facie obvious over the prior art.

Claims 1-10 and 17 are rejected under 35 USC 103(a) as being unpatentable over EP 0893440

Determining the scope and contents of the prior art

EP 0893440 discloses carvedilol of form I and II on page 3.

Brittain teaches us that it is a well known fact that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice." Thus, *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims. Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2).

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare the crystalline form as instantly claimed in claims 1-10 and 17 since the prior art reference discloses the formula of figure 1. One would be motivated to prepare the instantly claimed invention because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction patter, melting point etc. (see Brittian p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268 and Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant specification and claims claim a known compound, which is ***the same pure substance*** as the prior art, only *having different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p. 1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of

stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of known compounds would have been suggested to one skilled in the art. One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of the known compound would have been suggested to one skilled in the art. The compounds are of the same identical formula, the difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

The instant claims are claiming a product which is the same pure substance as the prior art, and only has different arrangements and/or different conformations of the molecules without any disclosure of any unexpected properties. The mere differences in the physical properties are well known conventional variations for the same pure substance and are prima facie obvious over the prior art.

Claims 1-10 and 17 are rejected under 35 USC 103(a) as being unpatentable over WO 99/05105.

Determining the scope and contents of the prior art

WO 99/05105 discloses carvedilol of form I and II on pages 5 and 6.

Brittain teaches us that it is a well known fact that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice." Thus, *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims. Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2).

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare the crystalline form as instantly claimed in claims 1-10 and 17 since the prior art reference discloses the formula of figure 1. One

would be motivated to prepare the instantly claimed invention because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction patter, melting point etc. (see Brittian p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268 and Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant specification and claims claim a known compound, which is ***the same pure substance*** as the prior art, only *having different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p. 1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of known compounds would have been suggested to one

skilled in the art. One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of the known compound would have been suggested to one skilled in the art. The compounds are of the same identical formula, the difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

The instant claims are claiming a product which is the same pure substance as the prior art, and only has different arrangements and/or different conformations of the molecules without any disclosure of any unexpected properties. The mere differences in the physical properties are well known conventional variations for the same pure substance and are prima facie obvious over the prior art.

Claims 1-10 and 17 are rejected under 35 USC 103(a) as being unpatentable over WO 02/00216.

Determining the scope and contents of the prior art

WO 02/00216 discloses crystalline carvedilol of form III, IV and V and the solvate of methyl-ethyl-ketone) on pages 5, 15 and 16.

Brittain teaches us that it is a well known fact that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice." Thus, *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims. Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2).

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare the crystalline form as instantly claimed in claims 1-10 and 17 since the prior art reference discloses the formula of figure 1. One would be motivated to prepare the instantly claimed invention because the instant

claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction patter, melting point etc. (see Brittian p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268 and Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant specification and claims claim a known compound, which is ***the same pure substance*** as the prior art, only *having different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p. 1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of known compounds would have been suggested to one skilled in the art. One skilled in the art would have been motivated to prepare different

crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of the known compound would have been suggested to one skilled in the art. The compounds are of the same identical formula, the difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

The instant claims are claiming a product which is the same pure substance as the prior art, and only has different arrangements and/or different conformations of the molecules without any disclosure of any unexpected properties. The mere differences in the physical properties are well known conventional variations for the same pure substance and are prima facie obvious over the prior art.

Claims 1-10 and 17 are rejected under 35 USC 103(a) as being unpatentable over US Pre-Grant Publication No. 2004152756.

Determining the scope and contents of the prior art

US Pre-Grant Publication No. 2004152756 discloses crystalline carvedilol form III on page 1.

Brittain teaches us that it is a well known fact that "many pharmaceutical solids exhibit polymorphism which is frequently defined as the ability of a substance to exist as two or more crystalline phases that have different arrangements and/or conformations of the molecules in the crystal lattice." Thus, *in the strictest sense, polymorphs are different crystalline forms of the* ***same pure substance*** *in which the molecules have different arrangements and/or different conformations of the molecules* (see Brittain p. 1-2).

Ascertaining the differences between the prior art and the claims at issue

The difference between the prior art and the instant claims is that the X-ray diffraction pattern the crystalline solid of the prior art may differ from that of the X-ray diffraction pattern of the instant claims. Brittain taught that "in the strictest sense, polymorphs are different crystalline forms of the same pure substance in which the molecules have different arrangements and/or different conformations of the molecules (see Brittain p. 1-2).

Resolving the level of ordinary skill in the pertinent art

However, minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art to prepare the crystalline form as instantly claimed in claims 1-10 and 17 since the prior art reference discloses the formula of figure 1. One would be motivated to prepare the instantly claimed invention because the instant claims differ from the known product merely by forms and the physical properties innate to the forms. As it was recognized in the art that in the pharmaceutical field, many solids exhibit polymorphism which is the innate nature of the particular drug (see US

Pharmacopia #23, national formulary #18). There is nothing unobvious about the innate nature of a drug. It is also recognized in the art that the innately existed different "morph" will display different physical properties such as X-ray diffraction patter, melting point etc. (see Brittian p. 178-179, 219). Just because it is "different" does not merit the new form patentability. As it was clearly stated by one having ordinary skill in the art in Brittain (p. 1-2) supra, as well as set forth by the court in In re Cofer 148 USPQ 268 and Ex parte Hartop 139 USPQ 525, that a product which are merely different forms of known compounds, notwithstanding that some desirable results are obtained therefrom, are unpatentable. The instant specification and claims claim a known compound, which is ***the same pure substance*** as the prior art, only *having different arrangements and/or different conformations of the molecule*. Mere difference in physical property is well known conventional variation for the same pure substance (see Brittain p. 1-2), i.e. prima facie obvious. For a known compound with defined chemical nature to be patentable for a new form, it must have a patentability basis of an advantage in terms of stability, formulation, solubility, bioavailability, ease of purification, preparation or synthesis, hydroscopicity, recovery or prevention of precipitation etc. (see p. 185).

Therefore, absent a showing of unobvious and superior properties, the instant claimed crystalline form of known compounds would have been suggested to one skilled in the art. One skilled in the art would have been motivated to prepare different crystalline forms of known pharmaceutically useful compounds with the expectation of obtaining a pharmaceutically useful benefit, such as longer shelf life, stability, enhanced deliverability, etc. Therefore, absent a showing of unobvious and superior properties,

the instant claimed crystalline form of the known compound would have been suggested to one skilled in the art. The compounds are of the same identical formula, the difference, if any, may reside in there being different crystalline forms. One of ordinary skill in the art would be motivated to prepare a different crystalline form of a known organic pharmaceutically active compound in the expectation of obtaining that very compound but with enhanced properties, e.g. improved solubility, shelf-life, improved mode of administering properties, etc. In the absence of a showing of a viable unexpected property (not just a difference in X-ray crystallography), the instant claimed invention is found obvious.

The instant claims are claiming a product which is the same pure substance as the prior art, and only has different arrangements and/or different conformations of the molecules without any disclosure of any unexpected properties. The mere differences in the physical properties are well known conventional variations for the same pure substance and are prima facie obvious over the prior art.

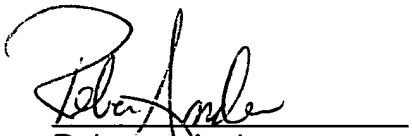
Conclusion

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Rebecca L. Anderson whose telephone number is (571) 272-0696. Mrs. Anderson can normally be reached Monday through Friday 5:30AM to 2:00PM.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Mr. Joseph K. McKane, can be reached at (571) 272-0699.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



August 30, 2006

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